REMARKS

Amendments to the Drawings

Applicants request that the originally filed drawings be replaced with formal drawing sheets of Figures 1-38 as submitted herewith. The drawings have been renumbered, as described below, and text has been deleted from several drawings and incorporated into the specification.

Amendments to the Specification

Applicants have amended the specification to insert SEQ ID NO identifiers to comply with the requirements set forth in 37 C.F.R. §§ 1.821 through 1.825, as well as to amend SEQ ID NO: 20 on page 61, line 18 of the specification. Namely, the DNA sequence has been updated to disclose the corresponding RNA strand. Support for correction of said error may be found in the corresponding description of the oligonucleotide (siRNA) as well as in the related SEQ ID NOs: 15-18 wherein the "target region" and "siRNA" are DNA and RNA sequences respectively. Applicants have also amended the specification to remove references to Figures 33-51, to insert text removed from the originally filed drawings, and to correct typographical errors.

Applicants request that any originally filed paper and CRF copies of the sequence listing be replaced with the substitute paper and CRF copies of the sequence listing submitted herewith.

Amendments to the Claims

Applicants have amended claims 40, 62, and 76 to delete the reference to PolyTran™ technology. Applicants have added new claims 77-85. Support for these

claims can be found in the specification as filed. For example, support for claim 77 can be found at page 18, lines 9-13; page 31, lines 7-29; page 36, lines 17-26. Support for claim 78 can be found at, for example, page 60, lines 1-7. Support for claim 79 can be found at, for example, page 30, lines 25-33. Support for claim 80 can be found at, for example, page 59, lines 14-17. Support for claims 81-83 can be found at, for example, page 30, lines 25-33; page 36, lines 24-26; and page 37, lines 2-11. Support for claims 84 and 85 can be found at, for example, page 60, lines 1-7.

Upon entry of the amendments, claims 33, 35-43, 51-52, 57-67, 70, 73-76, and 77-85 will be pending in this application.

No new matter is introduced by the amendments. Applicants request entry of the amendments and consideration and allowance of the claims.

Sequence Compliance – Notice to Comply

The Examiner states that the application fails to comply with the requirements set forth in 37 C.F.R. §§ 1.821 through 1.825. Specifically, the Examiner notes that Table III on page 92 of the specification contains sequences lacking sequence identifiers. A copy of the Notice to Comply is submitted herewith. Applicants have amended the specification and the claims to insert SEQ ID NO identifiers throughout the specification, including in Table III, in compliance with 37 C.F.R. § 1.821(d). Pursuant to the Notice to Comply, Applicants also submit herewith substitute paper and CRF copies of the sequence listing, an amendment requesting the entry of the sequence listing into the specification (see above), and a statement that the content of the paper and computer readable copies are the same and include no new matter, as required by

1.821(f) and 1.821(g). Applicants believe that the application now complies with the requirements set forth in 37 C.F.R. §§ 1.821 through 1.825.

Objection to the Drawings

The Examiner objects to the drawings because Figures 33-51 are missing. In the sole interest of moving this case toward allowance and without conceding the correctness of this objection, Applicants submit herewith corrected formal drawing sheets labeled "Replacement Sheet" in compliance with 37 C.F.R. § 1.121(d). Figures 52-57 have been renumbered as Figures 33-38, respectively. Applicants have amended references to the figure numbers in the specification for consistency. Applicants have also removed excessive text from the drawings and incorporated it into the specification.

Rejections under 35 U.S.C. § 112

I

Claims 40, 62, and 76 stand rejected under 35 U.S.C. § 112, second paragraph, for indefinite claim scope because these claims contain the trademark/trade name PolyTran™. In the sole interest of moving this case toward allowance and without conceding the correctness of this rejection, Applicants have amended claims 40, 62, and 76 to delete the reference to PolyTran™. Applicants request withdrawal of this rejection.

II

Claims 40, 62, and 76 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims recite a nucleic acid molecule that is associated with PolyTran™

technology. The Examiner considers the phrase "PolyTran™ technology" essential material to provide a written description of these claims. The Examiner further states that the specification does not provide a sufficient description of PolyTran™ technology. In the sole interest of moving this case toward allowance and without conceding the correctness of this rejection, Applicants have amended claims 40, 62, and 76 to delete the reference to PolyTran™ technology. Applicants request withdrawal of this rejection.

III

Claims 33, 35-43, 51, 52, 57-67, 70 and 73-76 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner acknowledges that the specification is enabling for methods for reducing breast cancer growth by intratumoral administration of an inhibitor of ICT1024 expression, but is of the view that it is not enabling for reducing growth of other cancers or use of other methods of administration. The Examiner states that the specification contemplates numerous routes of administration of inhibitors of ICT1024 expression and that problems related to the therapeutic use of nucleic acids were known in the art at the time of invention. The Examiner suggests that such problems included the inability to specifically deliver an effective concentration of a nucleic acid to a target cell such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. The Examiner states that the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression. The Examiner asserts that the specification and the teachings of the prior art do not provide this guidance. Applicants traverse.

ICT1024 is identified in the application, as filed, as human rhomboid family-1 (see, *e.g.*, page 34, lines 19-22). The application, as filed, demonstrates that silencing ICT1024 leads to apoptosis in cultured cells and to tumor shrinkage *in vivo* (see, *e.g.*, page 30, lines 25-32; page 36, line 24-26; Figures 4, 8, and 9). Applicants draw the Examiner's attention to Yan *et al.*, (2008) "Human rhomboid family-1 gene silencing causes apoptosis or autophagy to epithelial cancer cells and inhibits xenograft tumor growth" *Mol Cancer Ther*, 7:1355-1364 ("Yan", Exhibit A). Yan shows that siRNA molecules targeting the human rhomboid family-1 gene (RHBDF1) can be systemically delivered to MDA-MB-435 breast cancer and 1483 head and neck squamous cell carcinoma xenograft tumors in a mouse model and can cause a reduction in tumor volume after such delivery (see pages 1360-1362). According to Yan, the siRNA molecules were packaged in histidine and lysine polymers (see page 1357, left column) and delivered to the mice by tail vein injection (see page 1357, right column). Thus, Yan demonstrates that an inhibitor of ICT1024 can be delivered systemically *in vivo* to two different tumor xenografts in quantities sufficient to reduce ICT1024 expression. Yan also shows that this reduction in ICT1024 expression correlates with a reduction in tumor growth, as measured by tumor volume.

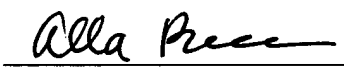
The delivery method described in Yan was contemplated by Applicants at the time of filing of the application and is part of the teaching of the specification. Polymers, such as the histidine and lysine polymer of Yan, are referred to in the specification as a possible delivery system (see, *e.g.*, page 42, lines 2-5) and described in International Application Publication WO 01/47496 (Exhibit B), which is cited in the specification (see, *e.g.*, page 18, line 31 and page 19, line 15-16) and which designates

the United States. The contents of WO 01/47496 were specifically and entirely incorporated incorporated by reference (see page 88, lines 15-17). The histidine and lysine polymer delivery systems thus were publicly available as of the priority date of this application by referring to these publications. Yan, thus, confirms the teaching of the application, as filed. Accordingly, the rejection under § 112, first paragraph (enablement), should be withdrawn.

CONCLUSION

Applicants request favorable consideration of the application and early allowance of the pending claims. To that end, the Examiner is invited to telephone the undersigned to discuss any issue pertaining to this reply.

Respectfully submitted,



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